NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Aquipta atogepant (as monohydrate) 10 mg tablets

Aquipta atogepant (as monohydrate) 60 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Aquipta 10 mg tablets: each tablet contains 10 mg of atogepant (as monohydrate)

Aquipta 60 mg tablets: each tablet contains 60 mg of atogepant. (as monohydrate)

Tablets contain mannitol.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Aquipta 10 mg tablets: White to off-white, round biconvex tablet debossed with “A” and “10” on one side.

Aquipta 60 mg tablets: White to off-white, oval biconvex tablet debossed with “A60” on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Aquipta is indicated for prophylaxis of migraine in adults who have at least 4 migraine days per month.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dose for Aquipta is 60 mg taken orally once daily with or without food.

Dose modifications

Dosing modifications for concomitant use of specific drugs are provided in Table 1.

Table 1: Dose modifications for drug interactions

Dosage modifications	Recommended once daily dose
Strong CYP3A4 inhibitors	10 mg
Strong OATP inhibitors	10 mg

Missed dose

A missed dose should be taken right away. If it is almost time for the next dose, patients should be instructed to skip the missed dose and take the next dose as scheduled.

Dosing in special populations

Elderly (>65 years)
Population pharmacokinetic modelling suggests no clinically significant pharmacokinetic differences between elderly and younger subjects. No dose adjustment of Aquipta is needed in elderly patients.

Hepatic impairment
Avoid use of Aquipta in patients with severe hepatic impairment. No dose adjustment is recommended for patients with mild or moderate hepatic impairment (see section 5.2 Pharmacokinetic properties).

Renal impairment
In patients with severe renal impairment (CLcr 15-29 mL/min), and in patients with end-stage renal disease (ESRD) (CLcr <15 mL/min), the recommended dosage of Aquipta is 10 mg once daily. For patients with ESRD undergoing intermittent dialysis, Aquipta should preferably be taken after dialysis. No dose adjustment is recommended for patients with mild or moderate renal impairment (see section 5.2 Pharmacokinetic properties).

Paediatric population
The safety and efficacy of atogepant in children have not yet been established. No data are available.

4.3 CONTRAINDICATIONS

Aquipta is contraindicated in patients with a history of hypersensitivity to atogepant or any of the components of Aquipta.

Reactions have included anaphylaxis and dyspnea (see section 4.4 Special Warnings and Precautions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Aquipta 10 mg tablets contain less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’. Aquipta 60 mg tablets contain 31.5 mg sodium per dose; this is equivalent to 1.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Hypersensitivity reactions, including anaphylaxis, dyspnea, rash, pruritus, urticaria, and facial edema, have been reported with use of Auipta (see section 4.8 Adverse effects (Undesirable effects)). Some hypersensitivity reactions can occur days after administration. If a hypersensitivity reaction occurs, discontinue Aquipta and institute appropriate therapy (see section 4.3 Contraindications).

Use in hepatic impairment

See Section 4.2 Dose and method of administration.

Use in renal impairment

See Section 4.2 Dose and method of administration.

Use in the elderly

See Section 4.2 Dose and method of administration.

Paediatric use

See Section 4.2 Dose and method of administration.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

CYP3A4 inhibitors

Co-administration of Aquipta with itraconazole, a strong CYP3A4 inhibitor, resulted in a significant increase (C_{max} by 2.15-fold and AUC by 5.5-fold) in exposure of atogepant in healthy subjects. The recommended dosage of Aquipta with concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) is 10 mg once daily. No dosage adjustment of Aquipta is needed with concomitant use of moderate or weak CYP3A4 inhibitors.

Physiologically based pharmacokinetic (PBPK) modelling suggested co-administration of Aquipta with moderate (e.g., cyclosporine, ciprofloxacin, fluconazole, fluvoxamine, grapefruit juice) or weak (e.g., cimetidine, esomeprazole) CYP3A4 inhibitors increase atogepant AUC by 1.7- and 1.1-fold, respectively. The changes in atogepant exposure when co-administered with weak or moderate CYP3A4 inhibitors are not expected to be clinically significant.

OATP inhibitors

Co-administration of Aquipta with single dose rifampicin, an OATP inhibitor, resulted in a significant increase in exposure of atogepant in healthy subjects. The recommended dosage of Aquipta with concomitant use of OATP inhibitors (e.g., cyclosporine) is 10 mg once daily.

Other drug interaction evaluations

Co-administration of Aquipta with oral contraceptive components ethinyl estradiol and levonorgestrel, famotidine, esomeprazole, paracetamol, naproxen, sumatriptan or topiramate did not result in significant pharmacokinetic interactions for either atogepant or co-administered drugs.

In Vitro studies

Enzymes

In vitro, atogepant is not an inhibitor for CYPs 3A4, 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6 at clinically relevant concentrations. Atogepant does not inhibit MAO-A or UGT1A1 at clinically relevant concentrations. Atogepant is not anticipated to be a clinically significant perpetrator of drug-drug interactions through CYP450s, MAO-A, or UGT1A1 inhibition.

Atogepant is not an inducer of CYP1A2, CYP2B6, or CYP3A4 at clinically relevant concentrations.

Transporters

Atogepant is a substrate of P-gp, BCRP, OATP1B1, OATP1B3, and OAT1. Dose adjustment for concomitant use of Aquipta with inhibitors of OATP is recommended based on a clinical interaction study with a OATP inhibitor.

Co-administration of atogepant with BCRP and/or P-gp inhibitors is not expected to increase the exposure of atogepant. Atogepant is not a substrate of OAT3, OCT2, or MATE1.

Atogepant is not an inhibitor of P-gp, BCRP, OAT1, OAT3, NTCP, BSEP, MRP3, or MRP4 at clinically relevant concentrations. Atogepant is a weak inhibitor of OATP1B1, OATP1B3, OCT1, and MATE1. No clinical drug interactions are expected for atogepant as a perpetrator with these transporters.

In Vivo Studies

CYP3A4 Inducers

Co-administration of Aquipta with rifampicin, a strong CYP3A4 inducer, decreased atogepant AUC by 60% and C_{max} by 30% in healthy subjects. No dedicated drug interaction studies were conducted to assess concomitant use with moderate CYP3A4 inducers. Moderate inducers of CYP3A4 can decrease atogepant exposure. Clinically significant interaction was not observed with concomitant administration of Aquipta and topiramate, a weak inducer of CYP3A4.

BCRP/OATP/P-gp Inhibitors

Co-administration of Aquipta with single dose rifampicin, an OATP inhibitor, increased atogepant AUC by 2.85-fold and C_{max} by 2.23-fold in healthy subjects.

Co-administration of Aquipta with quinidine, a P-gp inhibitor, increased atogepant AUC by 26% and C_{max} by 4% in healthy subjects. The changes in atogepant exposure when co-administered with P-gp inhibitors are not expected to be clinically significant.

PBPK modelling suggests that co-administration of Aquipta with BCRP inhibitors increases atogepant exposure by 1.2-fold. This increase is not expected to be clinically significant.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No human data on the effect of Aquipta on fertility are available. Animal studies showed no impact on female and male fertility with atogepant treatment.

Impairment of fertility

Oral administration of atogepant (0, 5, 20, or 125 mg/kg/day) to male and female rats prior to and during mating and continuing in females to Gestation Day 7 resulted in no adverse effects on fertility or reproductive performance. Plasma exposures (AUC) at the highest dose tested are approximately 15 times that in humans at the MRHD.

Use in pregnancy – Pregnancy Category B3

There are no data from the use of Aquipta in pregnant women. Studies in animals have shown reproductive toxicity. Aquipta is not recommended during pregnancy.

Oral administration of atogepant (0, 5, 15, 125, or 750 mg/kg/day) to pregnant rats during the period of organogenesis resulted in decreased foetal body weight and an increased incidence of foetal variations at the two highest doses tested (125 and 750 mg/kg) which was associated with maternal toxicity. At the no-effect dose (15 mg/kg/day) for adverse effects on embryofoetal

development, plasma exposure (AUC) was approximately 4 times that in humans at the maximum recommended human dose (MRHD) of 60 mg/day.

Oral administration of atogepant (0, 30, 90, or 130 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in no adverse effects on embryofoetal development. The highest dose tested (130 mg/kg/day) was associated with plasma exposures (AUC) approximately 8 times that in humans at the MRHD.

Oral administration of atogepant (0, 15, 45, or 125 mg/kg/day) to rats throughout gestation and lactation resulted in no adverse effects on development. Plasma exposure (AUC) at the highest dose tested is approximately 15 times that in humans at the MRHD.

Use in lactation.

It is unknown whether atogepant is excreted in human milk. Available toxicological data in animals have shown excretion of atogepant in milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Aquipta therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

In lactating rats, oral dosing with atogepant resulted in levels of atogepant in milk approximately 2 fold higher than those in maternal plasma.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Aquipta has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial experience

The safety of Aquipta was evaluated in 2657 patients with migraine who received at least one dose of Aquipta. Of these, 1225 patients were exposed to Aquipta for at least 6 months and 826 patients were exposed for 12 months.

In 12-week, placebo-controlled clinical studies, 314 patients received at least one dose of Aquipta 10 mg once daily, 411 patients received at least one dose of Aquipta 30 mg once daily, 343 patients received at least one dose of Aquipta 30 mg twice daily, 678 patients received at least one dose of Aquipta 60 mg once daily, 91 patients received at least one dose of Aquipta 60 mg twice daily, and 663 patients received placebo.

The most commonly reported adverse drug reactions were nausea (7%), constipation (7%), and fatigue/somnolence (5%). The majority of the cases were mild, and none were serious. The adverse reaction that most commonly led to discontinuation was nausea (0.6%).

Table 2 lists adverse reactions for which a causal relationship between Aquipta and the adverse event is at least a reasonable possibility.

The adverse reactions are listed below by system organ class and frequency. Frequencies are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000) or very rare (<1/10 000).

Table 2. Adverse drug reactions identified with Aquipta

System Organ Class	Frequency	Adverse Reaction
Immune system disorders	Not known	Hypersensitivity (e.g., rash, pruritus, urticaria, facial oedema)
Metabolism and nutrition disorders	Common	Decreased appetite
Gastrointestinal disorders	Common	Nausea, constipation
General disorders and administration site conditions	Common	Fatigue/somnolence

Liver Enzyme Elevations

In placebo-controlled studies, the rate of transaminase elevations over 3 times the upper limit of normal was similar between patients treated with Aquipta (0.9%) and those treated with placebo (1.2%). There were cases with transaminase elevations over 3 times the upper limit of normal that were temporally associated with Aquipta treatment; these were asymptomatic and resolved within 8 weeks of discontinuation. There were no cases of severe liver injury or jaundice in placebo-controlled studies.

Changes in body weight

In placebo-controlled studies, the proportion of patients with a weight decrease of at least 7% at any point was 2.5% for placebo, 3.8% for Aquipta 10 mg once daily, 3.2% for Aquipta 30 mg once daily, 5.3% for Aquipta 30 mg twice daily, 5.3% for Aquipta 60 mg once daily, and 6.8% for Aquipta 60 mg twice daily.

Post marketing Experience

The following adverse reactions have been identified during post-approval use of Auipta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: Hypersensitivity (e.g. anaphylaxis, dyspnea, rash, pruritus, urticaria, facial edema).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. In New Zealand, healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/submit-adverse-event.

4.9 OVERDOSE

There is no known antidote for Aquipta. Treatment of an overdose of Aquipta should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. For information on the management of overdose in New Zealand, contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Analgesics, antimigraine preparations.

ATC code: N02CD07.

Mechanism of action

Atogepant is an orally administered, small molecule, selective calcitonin gene-related peptide (CGRP) receptor antagonist that blocks the binding of the CGRP to the receptor and antagonizes CGRP receptor function. CGRP is a neuropeptide that has been associated with migraine pathophysiology. In the trigeminovascular system, CGRP modulates nociceptive signalling and inflammation, and also functions as a vasodilator.

Pharmacodynamic effects

Cardiac Electrophysiology

At a dose 5 times the maximum recommended daily dose, Aquipta does not prolong the QT interval to any clinically relevant extent.

Clinical trials

Aquipta was evaluated for the prophylaxis of migraine in two pivotal studies across the migraine spectrum in chronic and episodic migraine. The episodic migraine study (ADVANCE) enrolled patients who met International Classification of Headache Disorders (ICHD) criteria for a diagnosis of migraine with or without aura. The chronic migraine study (PROGRESS) enrolled patients who met ICHD criteria for chronic migraine. Both studies excluded patients with myocardial infarction, stroke, or transient ischemic attacks within six months prior to screening.

Episodic Migraine (Study 1 - ADVANCE)

Aquipta was evaluated for the prophylaxis of episodic migraine (4 to 14 migraine days per month) in a randomized, multicentre, double-blind, placebo-controlled study. A total of 458 patients were randomized 1:1 to receive Aquipta 60 mg (N = 235) or placebo (N = 223) once daily for 12 weeks. Patients were allowed to use acute headache treatments (i.e., triptans, ergotamine derivatives, nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen and opioids) as needed.

A total of 88% patients completed the 12-week double-blind study period. Patients had a mean age of 42 years (range: 18 to 73 years), 89% were female, and 83% were White. The mean migraine

frequency at baseline was approximately 8 migraine days per month and was similar across treatment groups.

The primary efficacy endpoint was the change from baseline in mean monthly migraine days (MMD) across the 12-week treatment period. Additional endpoints included the change from baseline in mean monthly headache days, the change from baseline in mean monthly acute medication use days, the proportion of patients achieving at least a 50% and 75% reduction from baseline in mean MMD (3-month average), and change from baseline at week 12 for Headache Impact Test (HIT-6) total score and Migraine Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) Role Function-Restrictive (RFR) domain score.

The HIT-6 measures the impact of headache on participants' ability to function at work, school, home, and in social situations. A reduction in scores from baseline indicates improvement. The MSQ v2.1 RFR domain score assesses how often migraine impacts function related to daily social and work-related activities over the past 4 weeks. An increase in scores from baseline indicates improvement.

Aquipta treatment demonstrated statistically significant improvements for key efficacy endpoints compared to placebo in Study 1, as summarized in Table 3.

Table 3: Efficacy endpoints in Study 1

	Aquipta 60 mg N=226	**Placebo N=216**
Monthly Migraine Days (MMD) across 12 weeks		
Baseline	7.8	7.5
Mean change from baseline	-4.1	-2.5
Difference from placebo	-1.7	
p-value	<0.001	
Monthly Headache Days across 12 weeks		
Baseline	9.0	8.5
Mean change from baseline	-4.2	-2.5
Difference from placebo	-1.7	
p-value	<0.001	
Monthly Acute Medication Use Days across 12 weeks		
Baseline	6.9	6.5
Mean change from baseline	-3.8	-2.3
Difference from placebo	-1.4	
p-value	<0.001	
≥ 50% MMD Responders across 12 weeks		
% Responders	59	29
Difference from placebo (%)	30	
p-value	<0.001	
≥ 75% MMD Responders across 12 weeks		
% Responders	38	11
Difference from placebo (%)	27	
p-value	<0.001[a]	
HIT-6[b] at week 12		
Baseline	63.8	64.6
Mean change from baseline	-9.1	-5.2

Difference from placebo	-3.9	
p-value	<0.001[a]	
MSQ v2.1 RFR[c] at week 12		
Baseline	46.6	46.6
Mean change from baseline	31.0	20.0
Difference from placebo	11.0	
p-value	<0.001	

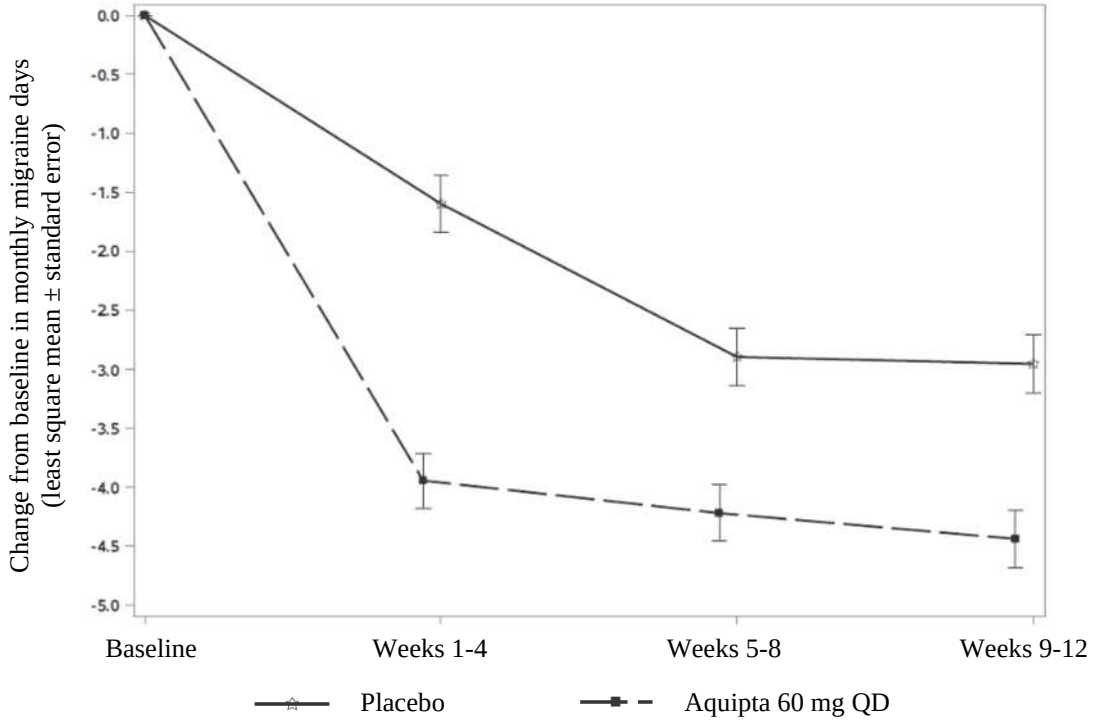
[a] Not adjusted for multiple comparisons
[b] Headache Impact Test total score
[c] Migraine Specific Quality of Life Questionnaire version 2.1 Role Function-Restrictive domain score

Additional pre-specified exploratory endpoints included the Activity Impairment in Migraine-Diary (AIM-D) domains and the MSQ v2.1 Role Function-Preventive (RFP) and Emotional Function (EF) domains. The AIM-D evaluates difficulty with performance of daily activities (PDA domain) and physical impairment (PI domain) due to migraine. A reduction in scores from baseline indicates improvement. MSQ v2.1 assesses how migraine prevents daily social and work-related activities (RFP domain) and the emotions associated with migraine (EF domain). An increase in scores from baseline indicates improvement.

The mean change from baseline for the AIM-D PDA domain (placebo: -6.1, 60 mg: -9.1) and AIM-D PI domain (placebo: -4.0, 60 mg: -6.4) demonstrated greater improvements with Aquipta across the 12-week treatment period. The change was significant when adjusted for multiple comparisons. At week 12, the mean change from baseline for the MSQ v2.1 RFP domain (placebo: 16.9, 60 mg: 23.9) and EF domain (placebo: 18.2, 60 mg: 28.8) demonstrated greater improvements with Aquipta (not controlled for multiple comparisons).

Figure 1 shows the mean change from baseline in MMD in Study 1. Patients treated with Aquipta had greater mean decreases from baseline in MMD across the 12-week treatment period compared to patients who received placebo. During the first month of treatment (starting the first day after the initial dose), Aquipta had greater mean decreases from baseline in weekly migraine days compared to placebo-treated patients.

Figure 1: Change from baseline in monthly migraine days in Study 1



In patients failing one or more prophylactic pharmacotherapies, the treatment difference for the reduction of MMD observed as compared to placebo across the 12-week treatment period was -2.2 (95% CI: -3.0, -1.3) for Aquipta 60 mg.

The proportions of participants with ≥ 50%, ≥ 75%, and 100% reduction in monthly migraine days was greater in the Aquipta treatment group than in the placebo treatment group for each of the 4-week intervals assessed (Weeks 1 to 4, 5 to 8, and 9 to 12), and the percentage of responders at each threshold increased over time.

Table 4: Reduction of ≥ 50%, ≥ 75%, and 100% from baseline in MMD by 4-week interval[a]

	Aquipta 60 mg (%)	**Placebo (%)**
≥ 50% MMD Responders		
Weeks 1-4	59	27
Weeks 5-8	66	46
Weeks 9-12	71	44
≥ 75% MMD Responders		
Weeks 1-4	39	10
Weeks 5-8	40	17
Weeks 9-12	49	22
100% MMD Responders		
Weeks 1-4	19	4
Weeks 5-8	24	8
Weeks 9-12	27	12

[a] $p < 0.001$ for all comparisons between Aquipta 60 mg and placebo (not adjusted for multiple comparisons)

Long-term efficacy (Study 1)

Efficacy was sustained for up to 1 year in an open-label study in which patients with episodic migraine received Aquipta 60 mg once daily. 68.4% of patients completed the treatment period. The reduction in the least-squares mean number of monthly migraine days in the first month (Weeks 1-4) was -3.8 days and improved to a least-squares mean reduction of -5.2 days in the last month (Weeks 49-52). Approximately 84%, 70%, and 48% of patients reported ≥ 50%, ≥ 75%, and 100% reduction in monthly migraine days at Weeks 49-52, respectively.

Chronic Migraine (Study 2 - PROGRESS)

Aquipta was evaluated for the prophylaxis of chronic migraine (15 or more headache days per month with at least 8 migraine days) in a randomized, multicentre, double-blind, placebo-controlled study. A total of 521 patients were randomized 1:1 to receive Aquipta 60 mg (N = 262) or placebo (N = 259) once daily for 12 weeks. A subset of patients (11%) was allowed to use one concomitant migraine prophylaxis medication (e.g., amitriptyline, propranolol, topiramate). Patients were allowed to use acute headache treatments (i.e., triptans, ergotamine derivatives, NSAIDs, acetaminophen and opioids) as needed. Patients with acute medication overuse and medication overuse headache also were enrolled.

A total of 463 (89%) patients completed the 12-week double-blind study. Patients had a mean age of 42 years (range: 18 to 74 years), 87% were female, and 60% were White. The mean migraine frequency at baseline was approximately 19 migraine days per month and was similar across treatment groups.

The primary efficacy endpoint was the change from baseline in mean MMD across the 12-week treatment period. Additional endpoints included the change from baseline in mean monthly headache days, the change from baseline in mean monthly acute medication use days, the proportion of patients achieving at least a 50% and 75% reduction from baseline in mean MMD (3-month average), and change from baseline at week 12 for HIT-6 total score and MSQ v2.1 RFR domain score.

Key efficacy results of Study 2 are summarized in Table 5.

Table 5: Efficacy endpoints in Study 2

	Aquipta 60 mg N=257	**Placebo N=249**
Monthly Migraine Days (MMD) across 12 weeks		
Baseline	19.2	19.0
Mean change from baseline	-6.8	-5.1
Difference from placebo	-1.7	
p-value	0.002	
Monthly Headache Days across 12 weeks		
Baseline	21.5	21.4
Mean change from baseline	-6.9	-5.2
Difference from placebo	-1.7	
p-value	0.002	
Monthly Acute Medication Use Days across 12 weeks		
Baseline	15.5	15.3
Mean change from baseline	-6.2	-4.1

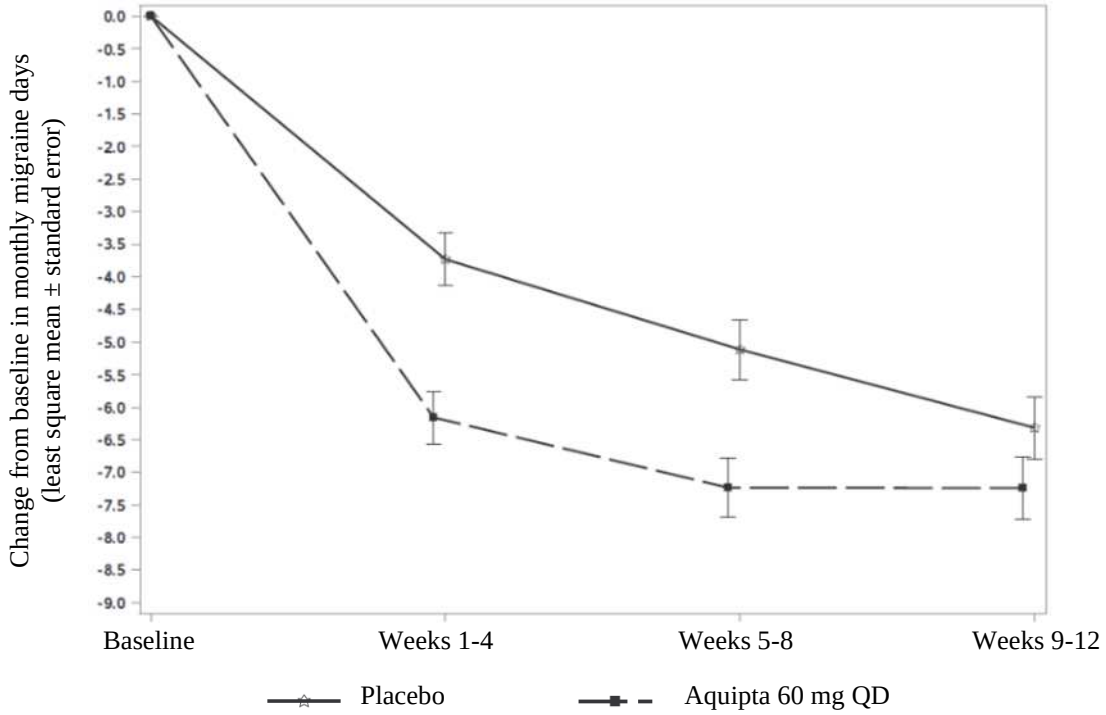
Difference from placebo	-2.1	
p-value	0.002	
≥ 50% MMD Responders across 12 weeks		
% Responders	40	27
Difference from placebo (%)	14	
p-value	0.002	
≥ 75% MMD Responders across 12 weeks		
% Responders	18	6
Difference from placebo (%)	13	
p-value	<0.001[a]	
HIT-6[b] at week 12		
Baseline	64.4	63.8
Mean change from baseline	-7.8	-5.2
Difference from placebo	-2.7	
p-value	0.002	
MSQ v2.1 RFR[c] at week 12		
Baseline	43.3	44.1
Mean change from baseline	23.1	17.3
Difference from placebo	5.8	
p-value	0.002	

[a] Not adjusted for multiple comparisons
[b] Headache Impact Test total score
[c] Migraine Specific Quality of Life Questionnaire version 2.1 Role Function-Restrictive domain score

Additional pre-specified exploratory endpoints included the MSQ v2.1 RFP and EF domains. The mean change from baseline for the MSQ v2.1 RFP domain (placebo: 13.6, 60 mg: 19.9) and EF domain (placebo: 15.7, 60 mg: 22.4) demonstrated greater improvements with Aquipta at week 12 (not controlled for multiple comparisons).

Figure 2 shows the mean change from baseline in MMD in Study 2. Patients treated with Aquipta had a greater mean decrease from baseline in MMD across the 12-week treatment period compared to patients who received placebo.

Figure 2: Change from Baseline in monthly migraine days in Study 2



In patients failing one or more prophylactic medications with the same mechanism of action, the treatment difference for the reduction of MMD observed between Aquipta 60 mg and placebo across the 12-week treatment period was -1.5 (95% CI: -3.3, 0.4). In patients failing two or more prophylactic medications with different mechanisms of action, the treatment difference was -2.4 (95% CI: -4.2, -0.6).

The proportions of participants with ≥ 50%, ≥ 75%, and 100% reduction in monthly migraine days was greater in the atogepant treatment group than in the placebo treatment group for each of the 4-week intervals assessed (Weeks 1 to 4, 5 to 8, and 9 to 12), and the percentage of responders at each threshold increased over time.

Table 6: Reduction of ≥ 50%, ≥ 75%, and 100% from baseline in MMD by 4-week interval

	Aquipta 60 mg (%)	Placebo (%)
≥ 50% MMD Responders		
Weeks 1-4	39[a]	18
Weeks 5-8	43[a]	31
Weeks 9-12	44	38
≥ 75% MMD Responders		
Weeks 1-4	17[a]	5
Weeks 5-8	24[a]	10
Weeks 9-12	28[a]	15
100% MMD Responders		
Weeks 1-4	4[b]	0
Weeks 5-8	6[a]	<1
Weeks 9-12	7[b]	3

[a] $p < 0.01$ for comparison between Aquipta 60 mg and placebo (not adjusted for multiple comparisons)
[b] $p < 0.03$ for comparison between Aquipta 60 mg and placebo (not adjusted for multiple comparisons)

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration of Aquipta, atogepant is rapidly absorbed with plasma concentrations >14 nM (EC_{90} based on capsaicin induced dermal vasodilation model [CIDV]) within 0.5 hours and median T_{max} values ranging from 1 to 2 hours. Atogepant displays dose-proportional pharmacokinetics through 300 mg single dose with no accumulation upon once daily dosing.

Effect of food

When Aquipta was administered with a high-fat meal, the food effect was not significant (AUC and C_{max} were reduced by approximately 18% and 22%, respectively, with no effect on median time to maximum atogepant plasma concentration). Aquipta was administered without regard to food in clinical efficacy studies.

Distribution

Plasma protein binding of atogepant was not concentration-dependent in the range of 0.1 to 10 µM; the unbound fraction of atogepant was approximately 4.7% in human plasma. The mean apparent volume of distribution of atogepant (Vz/F) after oral administration is approximately 292 L.

Metabolism

Atogepant is eliminated mainly through metabolism, primarily by CYP3A4. The parent compound (atogepant), and a glucuronide conjugate metabolite (M23) were the most prevalent circulating components in human plasma.

Excretion

The elimination half-life of atogepant is approximately 11 hours. The mean apparent oral clearance (CL/F) of atogepant is approximately 19 L/h. Following single oral dose of 50 mg ^{14}C-atogepant to healthy male subjects, 42% and 5% of the dose was recovered as unchanged atogepant in faeces and urine, respectively.

Specific populations

Patients with Renal Impairment

The renal route of elimination plays a minor role in the clearance of atogepant. Based on PBPK and population pharmacokinetic analysis, there is no significant difference in the pharmacokinetics of atogepant in patients with mild or moderate renal impairment (CLcr 30-89 mL/min) relative to those with normal renal function (CLcr ≥90 mL/min). As patients with severe renal impairment or end-stage renal disease (ESRD; CLcr <30 mL/min) have not been studied, use of the lowest effective dosage of Aquipta (10 mg) is recommended in those patients.

Patients with Hepatic Impairment

In patients with pre-existing mild (Child-Pugh Class A), moderate (Child-Pugh Class B), or severe hepatic impairment (Child-Pugh Class C), total atogepant exposure was increased by 24%, 15% and 38%, respectively. However, unbound atogepant exposure was approximately 3-fold higher in patients with severe hepatic impairment. Avoid use of Aquipta in patients with severe hepatic impairment.

Other Specific Populations

Based on a population pharmacokinetic analysis, age, sex, race, and body weight did not have a significant effect on the pharmacokinetics (C_{max} and AUC) of atogepant. Therefore, no dose adjustments are warranted based on these factors.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Atogepant was negative in *in vitro* (Ames, chromosomal aberration test in Chinese Hamster Ovary cells) and *in vivo* (rat bone marrow micronucleus) assays.

Carcinogenicity

Atogepant was administered orally to mice (0, 5, 20, or 75 mg/kg/day in males; 0, 5, 30, or 160 mg/kg/day in females) and rats (0, 10, 20, or 100 mg/kg in males; 0, 25, 65, or 200 mg/kg in females) for up to 2 years. There was no evidence of drug-related tumours in either species. Plasma exposures at the highest doses tested in mice and rats were approximately 8 and 20-35 times, respectively, that in humans at the maximum recommended human dose (MRHD) of 60 mg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets contain the following inactive ingredients: Copovidone, Tocofersolan, Mannitol, Microcrystalline cellulose, Sodium chloride, Croscarmellose sodium, Silicon dioxide and Sodium stearyl fumarate

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Aquipta 10 mg and 60 mg tablets: 36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. This medicinal product does not require any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER

Aquipta 10 mg tablets: White to off-white, round biconvex tablet debossed with “A” and “10” on one side.

Aquipta 60 mg tablets: White to off-white, oval biconvex tablet debossed with “A60” on one side.

The following presentations are available:

Monthly Pack 10 mg (28 tablets) - 1 carton containing four blister strips of PVC/PE/PCTFE Aclar® laminated blisters with aluminum foil lidding. Each blister strip contains 7 tablets with one tablet per blister cavity.

Starter Pack 60 mg (7 tablets) - 1 carton containing one blister strip of PVC/PE/PCTFE Aclar® laminated blister with aluminum foil lidding. The blister strip contains with 7 tablets with one tablet per blister cavity.

Monthly Pack 60 mg (28 tablets) - 1 carton containing four blister strips of PVC/PE/PCTFE Aclar® laminated blisters with aluminum foil lidding. Each blister strip contains 7 tablets with one tablet per blister cavity.

Not all presentations may be marketed.

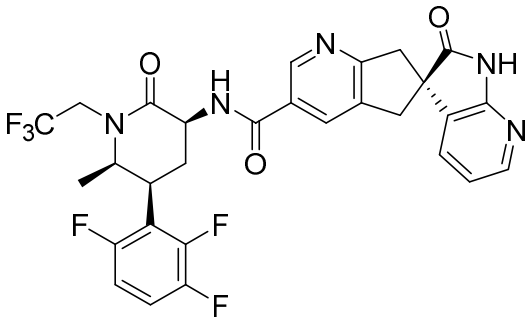
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In New Zealand, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical structure of atogepant is:



CAS number

1374248-81-3

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

AbbVie Limited

6th Floor, 156-158 Victoria St

Wellington, 6011

NEW ZEALAND

PH: 0800 900 030

9 DATE OF FIRST APPROVAL

30 May 2024

10 DATE OF REVISION

02 Aug 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.3	The risk of anaphylaxis and dyspnea has been included.
4.4	Information about hypersensitivity reactions has been added.

4.8	Post marketing adverse effects hypersensitivity included. ADR reporting URL revised